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08/981,310

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/981,310	12/16/97	LANDEGREN	U 1209-121P

HM32/0911  
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EXAMINER	
PORTNER, V	
ART UNIT	PAPER NUMBER

1641

DATE MAILED: 09/11/98

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12-16-97

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-8 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 1-8 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s) 6

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

- SEE OFFICE ACTION ON THE FOLLOWING PAGES -

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### **DETAILED ACTION**

Claims 1-8 are pending.

#### ***Priority***

1. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. PCT/SE96/00779, filed on June 14, 1996.

#### ***Information Disclosure Statement***

2. The information disclosure statement has been made of record and considered prior to this action.

#### ***Sequence Letter***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a) (1) and (a) (2) (SEE page 7, paragraph 3 and 4). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.136. In no case may and applicant extend the period of response beyond the six

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month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

***Drawings***


3. This application has been filed with drawings which are acceptable, see attached PTO-948

***Claim Rejections - 35 U.S.C. § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

 Claims 1-8 recite the phrase “characterized in”; it is not clear what other characteristics are being claimed that are not recited in the claims.

Claim 6 recites the phrase “crosslinkable oligonucleotides”, wherein claim 7 recites the step of “a ligase is added”; it is not clear that the “crosslinkable oligonucleotides” of claim 6 are complimentary to one another and therefore the addition of ligase in step 7 would not result in a postive effect. Claim 8 recites the addition of “an oligonucleotide complementary to the

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crosslinkable oligonucleotides of claims 6 or 7; it therefore appears that the “crosslinkable oligonucleotides” of claim 6 are not complimentary to each other and would not ligate upon the addition of ligase to the immunoassay method. Clarification of the reagents being used is requested.

Claim 6 in section e) recites the phrase “amplifying said crosslinked oligonucleotides”; as the claim does not recite a crosslinking step it is not clear when or how the “crosslinkable oligonucleotides” became crosslinked. Clarification is requested.

Claim 1 recites an immunological test kit but claim 4 only recites oligonucleotides complementary to one another are present in the kit; therefore the kit is not an immunological test kit but a kit for molecular biological determinations as the kit does not contain an antibody.

Claim 3 recites a list of reagents, it is not clear whether these reagents are all in the kit or whether the recitation of the reagents are presented in improper Markush Group format. If the claim was intended to recite a Markush group, then the claim should recite the members using language such as--selected from the group consisting of--. It is not clear what components are contained in the kit as an assay format comprising all of the recited reagents is not taught.

***Claim Rejections - 35 U.S.C. § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by or in the alternative as being obvious over Urdea (US Pat. 5,656,731).

Urdea disclose nucleic acid-amplified immunoassay probes and kits comprising the reagents for this assay (col. 18, lines 10-26), wherein the immunoassay comprises a first immobilized reagent having affinity to a specific macromolecule, and a second and third affinity reagent specific for different determinants which are modified with a crosslinkable oligonucleotide. See all Figures. The individual units of the amplifier probe are ligated with a ligase such as T4 DNA or RNA ligase. The affinity reagent may be an antibody or a nucleic acid. Urdea disclose kits comprising a first immobilized affinity reagent, and second and third affinity reagents as well as a hybrid linker probe as well as buffers, wash solutions, control reagents and labeling probes . Urdea differs from the instantly claimed invention by failing to specifically claim kits comprising these reagents.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to compile the necessary reagents for carrying out the amplified immunoassays of Urdea because Urdea suggests the formulation of kits comprising the necessary reagents to conduct the assays and Urdea teaches the use of antibodies and nucleic acids as affinity reagents for the detection of an analyte, as well as reagents for crosslinking assay components. The person of ordinary skill in the art would have been motivated to compile the

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immunoassay components into kit form for the art recognized advantages of convenience and standardization of reagents, as well as for ease of commercialization the assay test as a kit.

8. Claims 1, 3-5 are rejected under 35 U.S.C. 102(e) as being anticipated by or in the alternative as being obvious over Birkenmeyer et al (US Pat. 5,667,974).

Birkenmeyer et al disclose the use of affinity reagents on the solid phase (see claims 1-8) comprising the reagents for this assay, wherein the assay comprises a first immobilized reagent having affinity to a specific macromolecule, and a second and third affinity reagent specific for different determinants which are modified with a crosslinkable oligonucleotide., wherein the use of ligase is used in the detection of the desired macromolecule. Birkenmeyer et al disclose that kits comprising the compositions described are provided by the invention but differs from the instantly claimed invention by failing to specifically claim kits comprising these reagents.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to compile the necessary reagents for carrying out the assay pf Birkenmeyer et al because Birkenmeyer et al suggests the formulation of kits comprising the necessary reagents to conduct the assays and Birkenmeyer et teaches the use of affinity reagents for the detection of an analyte, as well as reagents for crosslinking assay components. The person of ordinary skill in the art would have been motivated to compile the immunoassay components into kit form for the art recognized advantages of convenience and standardization of reagents, as well as for ease of commercialization the assay test as a kit.

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9. Claims 1, 3-5 are rejected under 35 U.S.C. 103(a) as being obvious over Nickerson et al (1992) or Delahunty et al (1995) or Kwok et al (1992) or Nilsson et al (1994)

Nickerson et al or Delahunty et al or Kwok et al or Nilsson et al disclose the use of affinity reagents on the solid phase comprising the reagents for this assay, wherein the assay comprises a first immobilized reagent having affinity to a specific macromolecule, and a second and third affinity reagent specific for different determinants which are modified with a crosslinkable oligonucleotide., wherein the use of ligase is used in the detection of the desired macromolecule. Nickerson et al or Delahunty et al or Kwok et al or Nilsson et al disclose the use of an antibody for the detection of a determinant which is in association with the target analyte but differs from the instantly claimed invention by failing to show the reagents used in the assay formulated into kits comprising these reagents.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to compile the necessary reagents for carrying out the assay of Nickerson et al or Delahunty et al or Kwok et al or Nilsson et al because all of the references teach the use of affinity reagents for the detection of an analyte, as well as a reagent for crosslinking assay components and an immobilized affinity reagent and the person of ordinary skill in the art would have been motivated to compile the (immuno)assay components into kit form for the art recognized advantages of convenience and standardization of reagents, as well as for ease of commercialization the assay test as a kit.

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10. Claims 1-2 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al taken with Dattagupta et al (US Pat. 4,78,111).

Lee et al disclose an immunometric assay for antigenic substances using monoclonal antibodies on the solid phase and two or more monoclonals in a soluble labeled form. Various labels are disclosed such as fluorescent, radioactive and enzymatic labels but differs from the instantly claimed invention by failing to show the use of an oligonucleotide modified affinity reagent.

Dattagupta et al disclose the use nucleic acids as carriers for labels in association with antibodies in an analogous art for the purpose of providing a stable labeling reagent for immunoassays which provides a large number of labels for ease of detection and for highly sensitive immunoassays which are nonradioactive.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the detection reagent of Lee with the nucleotide label of Dattagupta because Dattagupta discloses that the nucleotide label is used in association with antibodies for the detection of antigens in an immunoassay format and Dattagupta teaches that the nucleic acid label provides a non-radioactive, highly convenient and sensitive way of labeling immunological reagents with multiple reagents(col. 2, lines 51-68), wherein the nucleotide labels would be crosslinkable. Therefore, the person of ordinary skill in the art would have been motivated to use the nucleic acid label of Dattagupta in place of the labels disclosed by Lee, and



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would have had a reasonable expectation of success because Dattagupta teaches means and methods of making the reagents which result in a highly convenient and sensitive immunoassay.

Lee taken with Dattagupta disclose reagents for the carrying out of immunoassays but differ from the instant invention by failing to show the formulation of the reagents into kit form.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to compile the necessary reagents for carrying out the immunoassay of Lee taken with Dattagupta because the references teach the use of affinity reagents for the detection of an analyte, as well as an immobilized affinity reagent and the person of ordinary skill in the art would have been motivated to compile the (immuno)assay components into kit form for the art recognized advantages of convenience and standardization of reagents, as well as for ease of commercialization the assay test as a kit.

11. Claims 3-5 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US Pat. 5,026,653) taken with Dattagupta as applied to claims 1-2 and 6 above and further in view of Ciechanover et al (US Pat. 5,384,255).

See discussion of Lee et al (US Pat. 5,026,653) taken with Dattagupta above. The cited references differ from the instantly claimed invention by failing to show the use of ligase chain reaction in the detection of an antigen.

Ciechanover et al means and methods for the detection of an antigen using antibodies detectably labeled with DNA in an analogous art for the purpose of detecting an antigen through

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immuno-polymerase chain reaction(col. 19, lines 48-49) amplification or ligase chain reaction (col. 19, line 65) methods. Ciechanover suggests the use of ligase chain reaction in conjunction with a DNA labeled antibody, wherein two or more oligonucleotides are ligated in the presence of a nucleic acid target having the sequence of the resulting di-oligonucleotide thereby amplifying the di-oligonucleotide.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify immunoassay format of Lee taken with Dattagupta in light of the teachings of Ciechanover et al because Ciechanover et al teach that DNA can readily be amplified many times to afford ready detection of antibody binding, as well as teaches the use of ligase chain reaction in which two or more oligonucleotides are ligated in the presence of a nucleic acid which affords the amplification of the di-nucleotide and aids in the detection process due to the amplified product being present. Therefore, the person of ordinary skill in the art would have been motivated to use a nucleic acid label which is readily amplified by polymerase chain reaction or ligase chain reaction because Ciechanover teaches that the DNA sequence can be amplified hundreds of times to produce hundreds of nanograms of product for the detection of an antigen, and the person of ordinary skill in the art would have had a reasonable expectation of success because Ciechanover teaches means and methods of making the reagents which result in a sensitive immunoassay.

It also would have been obvious to the person of ordinary skill in the art at the time the invention was made to compile the necessary reagents for carrying out the immunoassay of

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Lee taken with Dattagupta and Ciechanover because the references teach the use of affinity reagents for the detection of an analyte, as well as an immobilized affinity reagent and the use of ligase or DNA polymerase and the person of ordinary skill in the art would have been motivated to compile the (immuno)assay components into kit form for the art recognized advantages of convenience and standardization, as well as for ease of commercialization the assay test kit.

### *Conclusion*

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

13. Albarella et al (US Pat. 4,563,417) is cited to show the use of an immobilized reagent which has affinity for a macromolecule, which is used in association with antibodies and a nucleotide probe.

14. Bellet et al (US Pat. 5,011,771) is cited to show an immunoassay using three monoclonal antibodies for the detection of an analyte

15. Delahunty et al (1996) is cited to show DNA typing for human identification by PCR and by an oligonucleotide ligation assay.

16. Hari et al (US Pat. 5,079,172) is cited to show an immunoassay method which utilizes a crosslinking means for the detection of an analyte.

17. Haley et al (US Pat. 5,693,764) is cited to show nucleotide modified antibodies useful as diagnostics.

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18. Lizardi et al (WO94/16105) is cited to show RNA assays using probes and ribozyme ligase.
19. Lagerstrom et al (1991) is cited to show the efficient amplification of DNA fragments adjacent to a known sequence in human and YAC DNA.
20. Landegren (1992) is cited to show means for detection of mutations in Human DNA.
21. Landergren (1993) is cited to show ligation based DNA diagnostics
22. Samiotakis et al (1994) is cited to show a dual color detection method using ligase mediated analysis.
23. Samiotakis et al (1991) is cited to show a system for efficient genetic analysis using PCR using ligase mediated gene detection.
24. Tobe et al (1996) is cited to show a two color ELISA based oligonucleotide ligation assay.
- 25.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this group is (703) 308-4242.

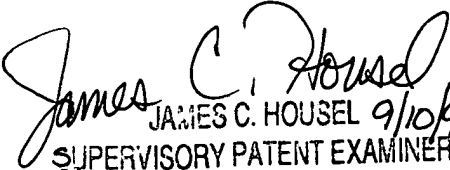
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The Group and/or Art Unit location of your application in the PTO will be changing February 7, 1998. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

August 25, 1998

  
JAMES C. HOUSEL 9/10/98  
SUPERVISORY PATENT EXAMINER